Remarks

Amendments to the Claims

Claim 1 was amended to clarify the claimed composition as including two elements:

One for intraoral administration, including a drug which can be intraorally administered, and

One for oral administration, including a drug which can be orally administered. This is discussed in more detail below.

Rejection Under 35 U.S.C. § 103

Claims 1-20, 22 and 23 were rejected as obvious under 35 U.S.C. 103(a) over U.S. Patent No. 6,294,199 to Conley et al. ("Conley"). Claim 21 was rejected as obvious under 35 U.S.C. 103(a) over Conley. Claim 1 was further rejected as obvious under 35 U.S.C. 103(a) over U.S. Patent No. 5,082,667 to Van Scoik ("Scoik") and Hackhs, Chemical Dictionary ("Hackhs"). The applicants respectfully traverse the rejections.

The claimed invention

Claims 1-19 and 22-23 are drawn to a pharmaceutical composition in dosage form for both intraoral and oral administration to a patient. The dosage form is configured to be placed intraorally in the patient. The dosage form includes (a) as a first releasing portion, a molded triturate tablet comprising a therapeutically effective amount of at least one pharmaceutically active ingredient capable of intraoral administration; and (b) as a second releasing portion located around the first portion as a compressed annular tablet, a therapeutically ingredient capable of oral administration and which is releasable and

orally ingestible by the patient after the molded triturate has disintegrated or has dissolved intraorally. Claim 20 is drawn to a process for the preparation of the unit dosage form, in which the second portion is provided as a single- or multi-layer compressed annular tablet, and then the first portion is molded as a triturate tablet into the annulus of the second portion. Claim 21 is drawn to a method of administering the unit dosage form to a patient. The method includes (1) placing the dosage form under the tongue or against the inner wall of the cheek or within the vestibular mucosa of the patient, (2) retaining the unit dosage form under the tongue or against the inner wall of the cheek or vestibular mucosa of the patient until the first releasing portion of the dosage form has dissolved or has disintegrated, and then (3) sucking or swallowing whole or chewing and swallowing the second releasing portion of the dosage form.

It is important to distinguish between the two components. The first releasing portion includes one or more active agents capable of intraoral administration. One of ordinary skill in the art would recognize, a drug administered orally would need to pass through the gut wall and liver, where a significant fraction of the drug would be metabolized (first pass metabolism), before the drug can exert its pharmacological effect (see also p. 10, lines 1-25). An intraoral composition of a drug capable of *intraoral* (i.e., within the mouth) administration allows the drug to avoid the first pass metabolism of the agent, thereby resulting in a higher bioavailability of the drug as compared to oral administration of the same drug. A higher bioavailability by introral administration of the drug results in an increased pharmacological effect of the drug or a reduction of the drug dosage to achieve the same level of pharmacological effect as the one achieved by oral administration of the drug.

However, not all drugs are intraorally available, just as not all drugs can be administered orally. Some drugs are not absorbed sufficiently through the mucosal lining of the mouth to be administered in this fashion, and may have to be administered orally. Conversely, some drugs are preferably administered in the mouth, where there is rapid uptake into the bloodstream, and cannot be given orally, due to destruction and delays in passage through the gastrointestinal tract (nitroglycerin being a well known example of such a drug).

The criteria for a drug to be administered intraorally include:

(1) the drug must have a molecular weight smaller than 350 (page 10, line 5);

(2) a small dose, 1 mcg to 50 mg, preferably 5 mcg to 40 mg and more preferably 10 mcg to 30 mg (page 9, lines 12-16);

(3) the drug must be solubilized rapidly in saliva in order to be absorbed.

Conley

Conley discloses an amoxycillin composition in which a first part of amoxycillin is formulated with pharmaceutically acceptable excipients which allow for immediate release of the first part of amoxycillin, to form an immediate release phase, and a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of the second part of amoxycillin, to form a **slow release phase** (col. 3, lines 45-52). The immediate release phase has a composition similar to that of known tablets which disintegrate immediately or rapidly (col. 11, lines 45-48). An alternative type of immediate release layer may be a swellable layer having a composition which incorporates polymeric materials which swell immediately and extensively in contact with water or aqueous media to form a water permeable but relatively large swollen mass

(col. 11, lines 61-65). The slow release phase has a composition containing amoxycillin together with a release retarding excipient which allows for slow release of amoxycillin (col. 12, lines 1-3). Suitable release retarding excipients include polymers such as pH sensitive polymer and some other crosslinked polymers provided at col. 12, lines 6-22. As Figure 2 shows, the slow release phase releases the second portion of amoxycillin over a time period of about seven hours following the release of amoxycillin in the immediate release phase.

Conley does not disclose a pharmaceutical composition which provides an immediate release portion for intraoral administration of a drug. Conley does not recognize the need to provide an immediate release portion for intraoral administration of a drug. This is hardly surprising in that Conley is drawn to administration of amoxycillin. It is well known that amoxycillin is stable in gastric environment. Amoxycillin is not a candidate for intraoral administration due to its large dose (more than 250 mg), large molecular weight (419) and low solubility in water (the USP states that amoxicillin is slightly soluble in water). Therefore, Conley does not provide motivation for one of ordinary skill in the art to make and use the claimed pharmaceutical composition.

The Examiner asserted that it would be obvious to one of ordinary skill in the art to optimize Conley's modified release formulation with the expectation of at least similar result because Conley teaches that the modified release formulation disclosed therein can be formulated into a chewable tablet, which allegedly suggests the active agent in the immediate release layer disintegrates rapidly in the mouth, and therefore, provides intraoral absorption. The applicants respectfully disagree.

A tablet can be chewed and swallowed for oral administration without being absorbed intraorally. A chewable tablet of a drug may allow some of the drug in the formulation to dissolve in mouth. However, intraoral administration of a drug requires more than disintegration of the tablet – it requires the drug to be capable of intraoral administration. To be capable of intraoral administration, a drug needs to be (1) sufficiently small and (2) to have certain chemical and physical properties, i.e., polarity and hydrophilicity/hydrophobicity, to pass and be absorbed at its therapeutically effective level through the mucous membranes of the oral cavity (see, p. 10, lines 3-5; p. 11, lines 15-21). Conley certainly fails to teach these two critical aspects of drugs suitable for intraoral administration. Therefore, Conley would not lead one of ordinary skill in the art to have a reasonable expectation of success of the claimed pharmaceutical composition.

Accordingly, Conley does not render any of claims 1- 23 obvious under 35 U.S.C. 103. See In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); see also MPEP §2143.

Scoik

Scoik describes a solid pharmaceutical dosage in triturate tablet form which dissolves quickly and masks the taste of the active ingredient (col. 2, lines 5-7). The tablet has discrete drug particles formed of a drug and melted triglyceride vehicle and carbohydrate by admixing the particles and carbohydrate and a temporary liquid binder (col. 2, lines 15-31). Scoik does not recognize the advantage and the need for intraoral administration of a drug. Nor does Scoik teach or define a drug suitable for intraoral administration – the ability of the drug to pass and be absorbed at its therapeutically

effective level through the mucous membranes of the oral cavity (see also the discussion of Conley).

Hackhs teaches that carbohydrates such as some starches, cellulose, and glycogens, can be active agents. Therefore, the Examiner asserted that Hackhs would suggest to one of ordinary skill in the art to incorporate one of these polysaccharides into the triturate dosage form of Scoik to make and use the formulation defined in claim 1. The applicants disagree. To one of ordinary skill in the art, starches, cellulose, glycogens and inulins are high molecular weight polymeric materials. One of ordinary skill in the art would recognize that these polymeric materials would not pass and certainly would not be absorbed at a therapeutically effective level through the mucus membrane of the oral cavities (see the discussion of molecular weights of the drug suitable for intraoral administration at p. 10, lines 3-5 of the present application).

Therefore, Soik and Hackhs in combination not only fail to provide motivation for one of ordinary skill in the art to make and use the formulation defined in claim 1, but also fail to lead one of ordinary skill in the art to have a reasonable expectation of success of the formulation of claim 1. Accordingly, Soik and Hackhs in combination do not make obvious the claimed formulation of claim 1 (*see, Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); *see also* MPEP § 2141).

U.S.S.N. 10/015,930
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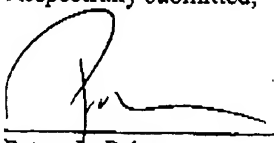
RESPONSE TO OFFICE ACTION

Allowance of all claims 1-23 are earnestly solicited.

Respectfully submitted,

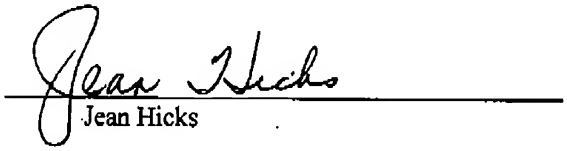


Patrea L. Pabst
Reg. No. 31,284

Date: May 28, 2003
Holland & Knight LLP
One Atlantic Center, Suite 2000
1201 W. Peachtree Street
Atlanta, GA 30309-3400
(404) 817 – 8473
(404) 817 – 8588 (fax)

CERTIFICATE OF FACSIMILE TRANSMISSION (37 CFR 1.8a)

I hereby certify that this Amendment and Response to Office Action, along with any paper referred to as being attached or enclosed, is being facsimile transmitted to the Commissioner for Patents, on the date shown below.



Jean Hicks

Date: May 28, 2003